Cell signaling researcher explores the frontiers of therapeutic potential

By Eddy Ball

NIEHS lead researcher Stephen Shears, Ph.D., opened his May 12 talk by describing its title as provocative. The presentation, "Cell Signaling by Inositol Pyrophosphates: Therapeutic Potential?" was part of the Laboratory of Signal Transduction Seminar Series, hosted by Perry Blackshear, M.D., D.Phil.

"IP7 kinases are involved in stimulating interferon transcription in response to viral infection," Shears told the audience. "The [signaling] pathways that are activated by viruses are also activated in metabolic inflammation, too. So these may also be relevant in diabetes and obesity." (Photo courtesy of Steve McCaw)

Although posed as a question, the fact that Shears could speak with confidence about therapeutic potential marks an important shift in thinking about inositol pyrophosphates (PP-IPs) and the enzymes, or kinases, that synthesize them. The PP-IPs are specialized members of the inositol phosphate (IP) cell signaling family.

New work by Shears' group and his collaborators has suggested that PP-IPs represent a target for therapy, to address several conditions triggered internally or by environmental exposures, such as viral infection, cancer, inflammation, diabetes, obesity, and aging-related diseases. Nevertheless, it is only in the past few weeks that anyone from the pharmaceutical industry has apparently paid much attention to PP-IP signaling.

"It [the title of this talk] was prompted by two communications I've had over the past three weeks or so [about the group's latest paper, *(http://www.ncbi.nlm.nih.gov/pubmed/24768307)* published online in April]," Shears said. "One was something I'd never even heard of before - the Science-Business eXchange *(http://www.nature.com/scibx/index.html)* - which is a kind of gateway between scientific communications and the pharmaceutical industry. And then a pharmaceutical company [Ono Pharma USA] *(http://www.ono.co.jp/eng/index.html)* came here a couple of weeks ago to talk about IP7 kinase [IP7K] and its possible therapeutic potential."

Moving from basic mechanisms to therapeutic targets

In the course of a publishing career that began in 1979, Shears has authored and co-authored nearly 150 papers, most of them studies on some aspect of IP metabolism that he and his colleagues have been the first to describe using biochemical, cell biological, and, more recently, structural approaches. As Shears explained, the synthesis of substrate analogues to inhibit IP kinases (IPKs) was complicated by chemical and electrical properties that made purification especially time-consuming.

An important step in drug discovery is to solve the crystal structure of suitable target enzymes. Then, drugs can be rationally designed to block the substrate-binding site. However, this is an especially challenging task with IPKs. When Shears and his group finally solved the structure of IP7K, they found a tight, highly specific binding pocket and a very unusual surface-mounted substrate binding site that acts as a funnel into the binding pocket.

"What we think is that this is a more flexible site, less specific, that acts to capture the substrate from the bulk phase and then transport it into the binding pocket," Shears said. One of the synthetic PP-IP analogues that Shears' collaborators synthesized was found to inhibit IP7K by blocking the substrate-capture site, rather than directly interfering with the catalytic pocket of the enzyme. Looking to work ahead, he suggested, "Maybe we can rationally design an inhibitor that is more hydrophobic and can get inside to actually inhibit the kinase."

The Shears group is also collaborating with scientists at the University of North Carolina at Chapel Hill, to test other synthetic substrates for manipulating IP7K activity with high-throughput screening.

Citation: Wang H, Godage HY, Riley AM, Weaver JD, Shears SB, Potter BV. *(http://www.ncbi.nlm.nih.gov/pubmed/24768307)* 2014. Synthetic inositol phosphate analogs reveal that PPIP5K2 has a surface-mounted substrate capture site that is a target for drug discovery. Chem Biol; doi:10.1016/j.chembiol.2014.03.009 [Online 23 April 2014].

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